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Serum Adiponectin and Coronary Heart Disease Risk in Older Black and White Americans

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Context: Adiponectin may influence the risk of coronary heart disease (CHD) independently of traditional cardiovascular risk factors.

Objective: Because body composition and adiponectin levels vary by race, we examined the relationship of adiponectin with prevalent and incident CHD in a cohort of older Black and White adults.

Design and Setting: We conducted a cross-sectional and prospective cohort study at two U.S. clinical centers.

Participants: Participants included 3075 well-functioning adults between ages 70 and 79 yr enrolled in the Health, Aging, and Body Composition study.

Main Outcome Measures: Prevalent CHD was defined as history of myocardial infarction, coronary artery bypass graft, percutaneous coronary transluminal angioplasty, angina, or major electrocardiogram abnormalities. After excluding those with prevalent CHD, incident CHD was defined as hospitalized myocardial infarction or CHD death.

Results: At baseline, 602 participants (19.6%) had CHD. During 6 yr of follow-up, 262 (10.6%) incident CHD events occurred. Whites had higher median adiponectin than Blacks (12 *vs.* 8 μg/ml, $P < 0.001$). Race modified the effect of adiponectin (P for interaction was 0.002 for prevalent CHD, and $P = 0.02$ for incident CHD). Among Whites, an inverse association of adiponectin with CHD was explained by high-density lipoprotein and glucose. Among Blacks, a doubling of adiponectin was associated with a 40% higher risk of both prevalent CHD (odds ratio, 1.41; 95% confidence interval, 1.11–1.78) and incident CHD (hazards ratio, 1.37; 95% confidence interval, 1.01–1.87) after adjusting for explanatory variables.

Conclusion: High circulating concentrations of adiponectin were associated with higher risk of CHD in older Blacks, even accounting for traditional CHD risk factors. **(*J Clin Endocrinol Metab* 91: 5044–5050, 2006)**

SEVERAL CYTOKINES AND cellular responses to inflammation have been implicated in the development of cardiovascular disease. Adipose tissue secretes a number of hormones, inflammatory proteins, and cytokines, collectively termed as adipocytokines, potentially linking obesity to insulin resistance and modulating the relationship between obesity and an increased risk of coronary heart disease (CHD).

Circulating levels of adiponectin, unlike other proteins secreted from adipose tissue, are lower in obese persons (1), those with type 2 diabetes (2), and in coronary artery disease (3, 4). Thus, adiponectin has been hypothesized to be an antidiabetic, antiatherosclerotic, and antiinflammatory hormone (5).

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; Health ABC, Health, Aging, and Body Composition; HR, hazards ratio; LDL, low-density lipoprotein; MI, myocardial infarction; OR, odds ratio; PTCA, percutaneous coronary transluminal angioplasty.

However, studies that have examined the relationship of adiponectin with incident CHD have yielded inconsistent results. A prospective study in White men reported a significant inverse association between plasma adiponectin levels and incident CHD (6, 7), whereas in a study of Native Americans, adiponectin was not associated with CHD (8). Ethnic differences in disease associations for adiponectin may exist because of biological differences in the determinants of and metabolic mechanisms by which adiponectin acts. Specifically, levels of total adiposity, visceral fat area, and lipid concentrations differ greatly between Blacks and Whites (9), and levels of circulating adiponectin are significantly lower in Black Americans than in Whites (10, 11); therefore, it is possible that adiponectin may differentially predict disease in these two racial groups. No studies have examined whether adiponectin is independently associated with CHD similarly among Black Americans and Whites.

To investigate this question, we examined the association between serum adiponectin among older White and Black men and women enrolled in the Health, Aging, and Body Composition (Health ABC) Study. We determined whether adiponectin was associated with prevalent or incident CHD

in the whole cohort and whether the relationship of adiponectin with CHD was modified by sex, race, level of adiposity, or other metabolic risk factors.

Subjects and Methods

Participants enrolled in the Health ABC study were well-functioning men and women between the ages of 70 and 79 yr who were recruited from April 1997 to June 1998 from a random sample of Medicare beneficiaries residing in the areas surrounding Pittsburgh, PA, and Memphis, TN. To be eligible for the study, participants had to report no difficulty in walking one quarter mile, climbing 10 steps, or performing basic activities of daily living. Individuals requiring assistive devices for ambulation, subjects with difficulty performing activities of daily living or life-threatening cancers, and those planning to leave the area within 3 yr were excluded from the study.

We first performed a cross-sectional study using the baseline data gathered in 1997–1998. We then performed a prospective analysis for incident CHD with a mean length of follow-up of 6.1 ± 1.8 yr.

The study was approved by the institutional review boards of the University of California, San Francisco, University of Pittsburgh, and University of Tennessee. All of the study participants provided written informed consent to participate in the study.

Racial group, age, and sex were assessed by self-report during the initial interview. On self-administered questionnaires, participants reported their average weekly alcohol consumption. Physical activity was assessed using self-report of walking and exercise, assigning kilocalories per week to activities (12). Participants reported smoking history as never, former, or current smoker. Each participant had seated systolic and diastolic blood pressures measured by a manual sphygmomanometer. Hypertension was defined by self-report of a diagnosis and use of an antihypertensive medication or if systolic blood pressure was at least 140 mm Hg or if diastolic blood pressure was at least 90 mm Hg. Diabetes was defined by self-report of diabetes diagnosis or use of diabetes drug or if fasting plasma glucose was at least 126 mg/dl or 2-h postchallenge glucose was at least 200 mg/dl. An intermediate category of glucose regulation comprising participants with impaired fasting glucose (100–125 mg/dl) (13) and/or impaired glucose tolerance (2-h postchallenge glucose between 140 and 200 mg/dl) (14) was created. Otherwise, the subjects were considered to have normal glucose tolerance.

Weight was measured on a standard balance beam scale and height by a stadiometer, and body mass index (BMI) was calculated. We measured visceral fat area by computed tomography scans using Somatom Plus 4 (Siemens, Erlangen, Germany), Picker PQ 2000S (Marconi Medical Systems, Cleveland, OH), or a 9800 Advantage scanner (General Electric, Milwaukee, WI) using standardized protocols. Visceral fat was measured at the L4–L5 level after participants were in the supine position. Visceral fat was manually distinguished from sc fat using the internal abdominal wall fascial plane, and fat area was calculated using interactive data language development software (RSI Systems, Boulder, CO).

Participants had venipuncture performed at the baseline visit after an overnight fast. Serum samples were frozen at −70 C and stored at McKesson BioServices, Rockville, MD. Fasting lipoprotein levels (Vitros 950 analyzer; Johnson & Johnson, New Brunswick, NJ), and fasting and 2-h postchallenge plasma glucose by automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; YSI, Yellow Springs, OH) were measured. Fasting serum insulin was measured by RIA (Pharmacia, Uppsala, Sweden) only among participants without known diabetes at the baseline examination.

Adiponectin was assayed in 2002–2003 from serum specimens that were frozen approximately 6–7 yr earlier. Total circulating levels of adiponectin were measured in duplicate by RIA (Linco Research, St. Charles, MO) with an intraassay coefficient of variation of 1.8–3.6%. Plasma high-sensitivity C-reactive protein (CRP) concentration was measured in duplicate by ELISA (Calbiochem, San Diego, CA) within 1 yr of specimen collection and was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/ml.

Outcomes

Prevalent CHD was defined using self-reported health history of prior coronary artery bypass surgery or percutaneous coronary transluminal angioplasty (PTCA), or prior myocardial infarction (MI) or angina and the use of an anti-anginal medication; hospitalizations for PTCA, coronary artery bypass graft, MI, or angina reported by the Centers for Medicare and Medicaid services between 1992 and 1998; and outpatient visits with PTCA, MI, or angina diagnoses between 1995 and 1998. We also used definite electrocardiogram evidence of previous MI with a major Q-wave abnormality to classify participants with prevalent CHD.

After excluding those with prevalent CHD, incident CHD was defined as any overnight hospitalization for MI or coronary death. Incident MI was determined by self-report at annual study assessment visits or during 6-month interim telephone follow-up assessments. All MI diagnoses were confirmed by review of hospital records for symptoms, electrocardiogram changes, and cardiac enzyme or troponin elevations. CHD death was defined as death from MI as the underlying cause, sudden death in the setting of a CHD history, or absence of an alternative cause based on review of medical records, death certificate, and an informant interview (15). Additionally, all hospitalizations and all deaths that occurred underwent a complete medical record review to capture any other cases of nonfatal or fatal CHD.

Statistical analysis

In preliminary analyses, univariate associations of baseline covariates with prevalent CHD were assessed using χ^2, t, and Wilcoxon tests as appropriate; for incident CHD, unadjusted Cox models were used for this step. We log transformed adiponectin, high-density lipoprotein (HDL)-cholesterol, fasting insulin, and CRP to meet linearity assumptions and rescaled abdominal visceral fat and BMI by their SD to compare associations with these predictors directly. We also assessed the correlation between adiponectin and other fat and metabolic variables overall and by race and sex.

We used multivariable logistic regression to examine adjusted associations between adiponectin and prevalent CHD and the Cox proportional hazards model for incident CHD. We examined the effects of adiponectin 1) after log transformation such that the resulting odds and hazard ratios estimate the effect of a doubling of adiponectin and 2) by quartiles. In nested sequences of models using log-transformed adiponectin, we first adjusted for age, sex, and study site. Next, we added all potential confounders, including current smoking, hypertension, low-density lipoprotein (LDL)-cholesterol, BMI, abdominal visceral fat, and medication use, thereby obtaining an estimate of the overall independent effect of adiponectin. Finally, we added potential mediators of the effects of adiponectin: glucose subgroup, HDL, CRP, and fasting insulin, in separate steps. This explanatory analysis provides an estimate of the direct effects of adiponectin via pathways other than through these mediators.

We examined whether the association of adiponectin with CHD varied by sex or race using the multivariate models adjusted for all potential confounders, but not including the potential mediators. Because we found striking evidence of an interaction by race, we repeated our nested sequences of models separately by race.

To check these models, we examined whether the race-specific associations of adiponectin with prevalent CHD were similar by sex, BMI categories, and visceral fat area. In the Cox models, the proportional hazards assumption was verified by examining plots of Schoenfeld residuals (16) *vs.* transformed time and by assessing interactions of all predictors with time. We used SAS version 8.2 (SAS Institute, Cary, NC) and SPlus version 6.1 (Insightful Corp., Seattle, WA) to perform the analyses.

Results

At baseline, 602 participants (20%) had CHD. White men had the highest prevalence of CHD (264 of 939, 28%) and White women had the lowest (101 of 855, 12%), whereas CHD prevalence for Black men was 22% (121 of 552) and for Black women was 16% (116 of 729). Baseline mean values and bivariate relationships with prevalent CHD are shown in supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://

jcem.endojournals.org. After excluding all individuals with prevalent CHD (n = 237), over an average 6.1 ± 1.8 yr of follow-up, 262 participants (10.6%) developed CHD. Of these events, only 32 (12%) were from CHD death. Overall, there was a slightly higher incidence of CHD among Whites compared with Blacks (18.7 *vs.* 15.2 per 1000 person-years, $P = 0.11$). Men had a higher incidence of CHD than women (23.1 *vs.* 12.8, $P < 0.001$). White men had the highest incidence (26.1) and White women the lowest (12.5). Incidence rates in Black men and women were 18.3 and 13.2, respectively.

We examined the correlation between serum adiponectin levels and several metabolic covariates. The correlations were modest and similar between racial groups. Among Whites, the Spearman correlation between adiponectin and BMI was −0.30, for abdominal visceral fat was −0.43, for HDL-cholesterol was 0.52, for CRP was −0.06, for fasting glucose was −0.35, and for fasting insulin was −0.40. For Black adults, the correlation between adiponectin and BMI was −0.22, for abdominal visceral fat was −0.35, for HDL-cholesterol was 0.45, for CRP was −0.13, for fasting glucose was −0.29, and for fasting insulin was −0.32.

We examined the bivariate association between the covariates and incident CHD by racial group (Table 1). Several metabolic variables such as BMI, abdominal visceral fat, LDL, triglycerides, and fasting insulin were similar between Blacks with and without incident CHD, whereas in Whites, these variables were more abnormal among those with CHD. Median values of total adiponectin did not differ between Blacks with and without CHD, whereas adiponectin levels were significantly lower among Whites who developed CHD compared with Whites without CHD.

To determine the association between adiponectin and prevalent and incident CHD, we constructed multivariable logistic regression models adjusting for traditional cardiac risk factors as well as all additional covariates and confounders associated with CHD. We found that the association between log adiponectin and prevalent and incident CHD was significantly stronger in Blacks (P for interaction = 0.002 for prevalent CHD, and $P = 0.02$ for incident CHD), but was similar in men and women. Therefore, we performed race-specific models.

Figure 1 displays the association of log adiponectin with prevalent CHD with sequential adjustment. In Whites, the initially protective association of adiponectin with prevalent CHD adjusting only for age, sex, and study site [odds ratio (OR), 0.78; 95% confidence interval (CI), 0.68–0.91) was attenuated after adjusting for traditional cardiac risk factors and other confounders. This was further attenuated after adjustment for variables potentially in the causal pathway

TABLE 1. Characteristics of the study population by race and incident CHD status

	Blacks (n = 1044)			Whites (n = 1429)		
	Incident CHD, n = 96	No CHD, n = 948	*P*	Incident CHD, n = 166	No CHD, n = 1263	*P*
Age (yr)	73.3 ± 3.0	73.3 ± 2.8	0.83	73.8 ± 3.0	73.7 ± 2.8	0.55
Female sex	50 (52.1)	563 (59.4)	0.17	61 (36.8)	693 (54.9)	<0.001
Study site						
Memphis, TN	46 (8.8)	476 (91.2)	0.67	76 (10.1)	676 (89.9)	0.06
Pittsburgh, PA	50 (9.6)	472 (90.4)		90 (13.3)	587 (86.7)	
Education, more than high school graduate	24 (25.0)	249 (26.3)	0.86	87 (52.4)	679 (53.8)	0.79
Current smoking	18 (18.8)	149 (15.7)	0.41	10 (6.0)	85 (6.7)	0.73
Alcohol use, ≥1 drink/wk	30 (31.3)	363 (38.3)	0.16	103 (62.1)	723 (57.2)	0.26
Physical activity (kcal/wk)[a]	217 (964)	240 (822)	0.88	708 (1802)	611 (1307)	0.38
Hypertension[b]	72 (75.0)	668 (70.5)	0.35	105 (63.3)	650 (51.5)	0.004
Glycemic status[b]						
Diabetes	37 (38.5)	244 (25.7)	0.04	47 (28.3)	196 (15.5)	0.001
Intermediate glucose regulation	19 (19.8)	259 (27.3)		46 (27.7)	384 (30.4)	
Normal glucose tolerance	39 (40.6)	391 (41.2)		73 (44.0)	644 (51.0)	
BMI (kg/m^2)	29.0 ± 5.1	28.6 ± 5.5	0.48	27.5 ± 4.0	26.3 ± 4.1	<0.001
Abdominal visceral fat area (cm^2)	141.2 ± 71.1	127.6 ± 60.8	0.08	163.0 ± 78.1	145.6 ± 66.4	0.007
LDL-cholesterol (mg/dl)	123.1 ± 34.2	124.8 ± 35.8	0.67	128.7 ± 33.7	120.6 ± 32.9	0.003
HDL-cholesterol (mg/dl)[a]	49.0 (15.0)	55.0 (21.0)	0.001	46.0 (17.5)	52.0 (21.0)	<0.001
Triglycerides (mg/dl)[a]	110.0 (70.0)	104.0 (53.0)	0.25	137.0 (94.0)	128.0 (80.0)	0.04
Fasting insulin (μIU/ml)[a]	7.9 (6.7)	7.5 (5.6)	0.56	7.4 (5.5)	6.2 (4.6)	0.006
CRP (mg/liter)[a]	2.4 (2.4)	2.0 (2.7)	0.41	1.7 (2.1)	1.5 (1.7)	0.20
Adiponectin (μg/ml)[a]	8.0 (7.0)	8.0 (7.0)	0.75	10.0 (8.0)	12.0 (9.0)	0.001
Medication use						
Aspirin	30 (31.3)	243 (25.6)	0.22	73 (44.0)	421 (33.3)	0.007
Statin	13 (13.5)	70 (7.4)	0.03	14 (8.4)	139 (11.0)	0.31
ACE inhibitor	22 (22.9)	144 (15.2)	0.05	22 (13.3)	139 (11.0)	0.39
Oral estrogen	6 (6.3)	68 (7.2)	0.74	17 (10.3)	228 (18.1)	0.01

The data exclude the 602 participants with prevalent CHD. All values represent n (%) or mean ± SD. *P* values were by χ^2 or *t* test where appropriate. ACE, angiotensin converting enzyme.

[a] Median (interquartile range) is reported for skewed variables, and *P* values are by Wilcoxon test.

[b] Hypertension defined as self-report of diagnosis and use of antihypertensive medication, or systolic blood pressure at least 140 mm Hg or diastolic blood pressure at least 90 mm Hg. Diabetes is defined by self-report of diabetes diagnosis, use of diabetes drug, fasting glucose of at least 126 mg/dl or 2-h postchallenge glucose of at least 200 mg/dl. Intermediate glucose regulation is defined if fasting glucose is 100–125 mg/dl or if 2-h glucose is between 140–200 mg/dl. Normal glucose regulation is classified otherwise.

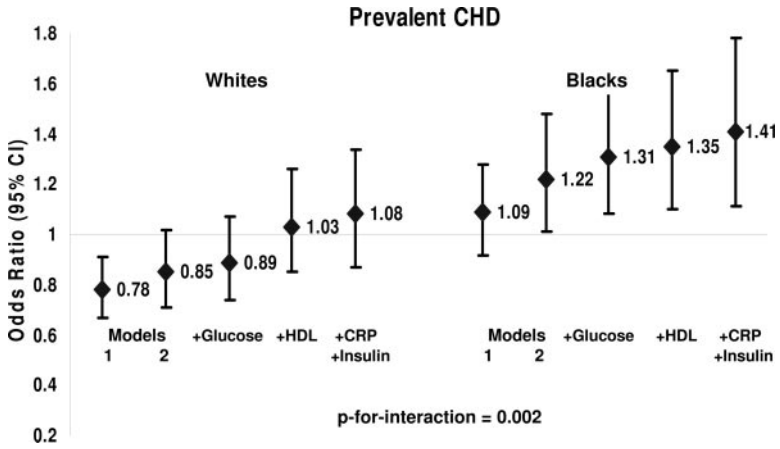

FIG. 1. Association between adiponectin and prevalent CHD with sequential adjustment by race. Model 1 is adjusted for age, sex, and study site. Model 2 is model 1 plus current smoking, hypertension, LDL, aspirin use, BMI, abdominal visceral fat, statin, oral estrogen, and angiotensin converting enzyme inhibitor use. Model 2 is then adjusted by glucose category, HDL-cholesterol, CRP, and fasting insulin.

including glucose, HDL-cholesterol, CRP, and fasting insulin (OR, 1.08; 95% CI, 0.87–1.34) (Table 2).

Among Blacks, log adiponectin was not significantly associated with prevalent CHD in the model adjusting only for age, sex, and study site (OR, 1.09; 95% CI, 0.92–1.29). However, after adjustment for traditional cardiac risk factors and other covariates, higher adiponectin was associated with prevalent CHD. After adjustment for the four variables potentially in the causal pathway between adiponectin and CHD, we found that a doubling of adiponectin was directly associated with a 40% increased odds of CHD in Blacks (OR, 1.41; 95% CI, 1.01–1.78) (Table 2).

In multivariate Cox models for incident CHD, we found a similar pattern of results for both Whites and Blacks as with the prevalent CHD outcome (Fig. 2). In Whites, the initially protective association between adiponectin and incident CHD was attenuated to a lesser degree than in the prevalent CHD models, with a hazards ratio (HR) of 0.85 (95% CI, 0.66–1.09) in the fully adjusted model. Among Blacks, a doubling of adiponectin was independently associated with an increased risk of incident CHD (HR, 1.37; 95% CI, 1.01–1.87) after adjusting for confounders and mediators (Table 2).

In Fig. 3, the fully adjusted odds of CHD for each quartile of adiponectin are shown separately by race. Because the distribution of adiponectin differed significantly by race, we used race-specific quartiles for these analyses. Among Whites, risk of both prevalent and incident CHD was similar across quartiles of adiponectin. In contrast, among Blacks, the odds of prevalent CHD were significantly elevated in the fourth quartile of adiponectin (≥12 μg/ml) compared with the first (OR, 2.53; 95% CI, 1.34–4.79); similarly, in the Cox model for incident CHD, we found a trend toward increased risk in the fourth quartile compared with the first (HR, 2.13; 95% CI, 0.91–4.95).

Finally, we examined whether the association of adiponectin with prevalent CHD differed by sex, BMI category, or abdominal visceral fat tertile separately by race. Because abdominal visceral fat was distributed differently by race, we used race-specific tertiles. The adverse association with higher adiponectin levels was observed only among Blacks

TABLE 2. Race-specific multivariate models for prevalent and incident CHD

	Prevalent CHD OR (95% CI)		Incident CHD HR (95% CI)	
	Blacks	Whites	Blacks	Whites
Log adiponectin	1.41 (1.11–1.78)	1.08 (0.88–1.34)	1.37 (1.01–1.87)	0.85 (0.66–1.09)
Age, per yr	1.10 (1.03–1.17)	1.03 (0.98–1.08)	0.99 (0.91–1.07)	1.03 (0.98–1.10)
Sex, female *vs.* male	0.62 (0.41–0.93)	0.44 (0.31–0.64)	0.73 (0.43–1.24)	0.56 (0.38–0.83)
Study site, Memphis *vs.* Pittsburgh	0.73 (0.51–1.04)	1.05 (0.78–1.41)	1.16 (0.72–1.86)	1.14 (0.80–1.61)
Current smoking	0.54 (0.31–0.94)	0.79 (0.41–1.50)	1.29 (0.70–2.35)	1.17 (0.61–2.25)
Hypertension	1.49 (0.95–2.33)	1.68 (1.23–2.28)	1.20 (0.70–2.04)	1.48 (1.05–2.09)
LDL, per mg/dl	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (0.99–1.01)	1.01 (1.00–1.01)
BMI, per SD kg/m^2	0.88 (0.70–1.11)	0.92 (0.73–1.17)	0.83 (0.61–1.12)	1.15 (0.89–1.50)
Abdominal visceral fat, per SD cm^2	1.14 (0.89–1.47)	0.96 (0.79–1.16)	1.19 (0.86–1.64)	0.84 (0.66–1.06)
Aspirin use	2.85 (1.99–4.07)	4.11 (3.07–5.49)	1.09 (0.65–1.82)	1.56 (1.12–2.18)
Statin use	3.42 (2.09–5.60)	3.20 (2.24–4.58)		
Oral estrogen use	0.66 (0.30–1.47)	0.56 (0.31–1.01)		
ACE inhibitor use	1.13 (0.72–1.78)	1.62 (1.11–2.37)		
Potential explanatory variables				
Glycemia categories (reference, normal glucose)				
Intermediate glucose regulation	0.91 (0.59–1.39)	1.02 (0.73–1.42)		
Diabetes	1.80 (1.15–2.83)	1.48 (0.99–2.20)	1.26 (0.70–2.25)	1.35 (0.88–2.05)
Log HDL	0.79 (0.38–1.62)	0.33 (0.18–0.61)	0.46 (0.18–1.17)	0.84 (0.41–1.74)
Log CRP	1.30 (1.06–1.60)	1.24 (1.04–1.48)	1.06 (0.80–1.40)	1.24 (1.00–1.53)
Log insulin	1.02 (0.71–1.47)	1.20 (0.89–1.63)	1.32 (0.84–2.06)	1.39 (0.96–1.99)

The incident CHD models are not adjusted for statin, oral estrogen, or angiotensin converting enzyme (ACE) inhibitor use because these variables were not associated with the outcome; the diabetes variable is dichotomous for the incident CHD model.

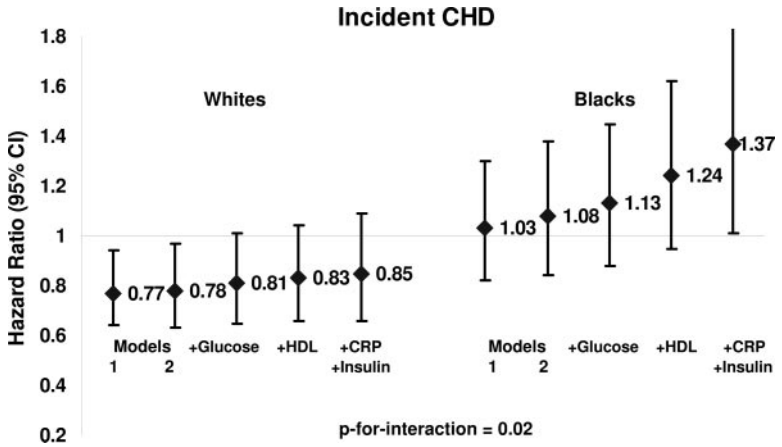

FIG. 2. Association between adiponectin and incident CHD with sequential adjustment by race. Model 1 is adjusted for age, sex, and study site. Model 2 is model 1 plus current smoking, hypertension, LDL, aspirin use, BMI, and abdominal visceral fat. Then, Model 2 is adjusted by glucose category, HDL, CRP, and fasting insulin in separate stages.

who were normal weight or overweight but not for those who were obese (OR, 1.58, 1.09–2.29 for BMI < 25 kg/m^2; OR, 1.99, 1.36–2.91 for BMI 25–29.9 kg/m^2; and OR, 0.83, 0.56–1.22 for BMI ≥ 30 kg/m^2, P for interaction = 0.002).

Discussion

Older White Americans had higher median serum levels of total adiponectin compared with older Blacks. Adiponectin was inversely associated with prevalent and incident CHD in White men and women, but this relationship was completely attenuated after adjustment for variables that potentially underlie the influence of adiponectin on CHD risk (HDL, inflammation/CRP, and glucose tolerance/insulin sensitivity). Paradoxically, among Black subjects, adiponectin was associated with a higher prevalence and incidence of CHD, such that a doubling of adiponectin was associated with an approximate 40% higher risk of CHD independently of known biological pathways. This association was most apparent in the highest quartile of adiponectin (>12 μg/ml) and among normal or overweight Black participants.

Adiponectin is a protein produced exclusively by adipocytes and is homologous to collagen VIII and X and complement factor C1q. Adiponectin circulates in a homotrimer form, a low-molecular-weight hexamer, and high-molecular-weight forms larger than 400 kDa (5), together accounting for 0.01% of total plasma protein (1). Commercially available assays, including the one used in the present study, measure total levels of circulating adiponectin. However, the ratio of the high-molecular-weight form/total circulating adiponectin (S_A) has been best correlated with improvements in insulin sensitivity and may therefore be the more sensitive indicator of the protective effect of this protein (17). Our finding of differential effects of adiponectin on CHD by race raises the possibility that Blacks and Whites may differ with respect to the proportions of the high-molecular-weight adiponectin relative to total adiponectin levels.

Data from animal and *in vitro* studies suggest several mechanisms by which adiponectin may affect atherosclerosis. *In vitro* studies show that adiponectin inhibits vascular adhesion factors in endothelial cells (18), inhibits foam cell formation (19), inhibits smooth muscle proliferation and migration (20), and suppresses growth and function of macrophages (19, 21). Animal studies have shown that mice lacking adiponectin have increased neointimal formation in response to vascular cuff injury (20, 22), and overexpression of the globular portion of adiponectin in a proatherogenic mouse model decreased the development of atherosclerosis (23).

Translating these laboratory findings to humans, early clinical studies also found inverse associations between adiponectin and CHD prevalence in Japanese men (18, 24, 25)

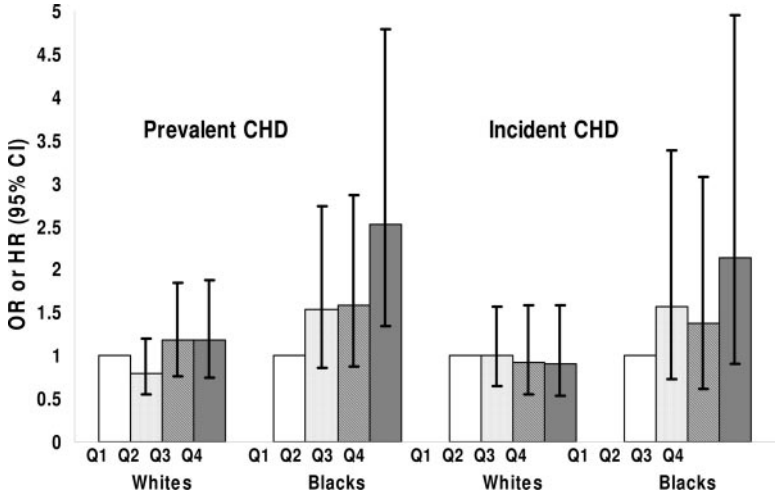

FIG. 3. Fully adjusted association of each adiponectin quartile and prevalent or incident CHD according to race. Adiponectin quartile ranges are as follows: Whites, Q1 < 8 μg/ml, Q2 = 8–11.9 μg/ml, Q3 = 12–15.9 μg/ml, Q4 $\geq$ 16 μg/ml; Blacks, Q1 < 5 μg/ml, Q2 = 5–7.9 μg/ml, Q3 = 8–11.9 μg/ml, and Q4 ≥ 12 μg/ml. The prevalent CHD model is adjusted for age, sex, study site, current smoking, hypertension, LDL-cholesterol, aspirin use, statin, oral estrogen, angiotensin converting enzyme inhibitor use, BMI, abdominal visceral fat area, glucose categories (normal, intermediate, and diabetes), HDL-cholesterol, CRP, and fasting insulin. The incident CHD model is adjusted for age, sex, study site, current smoking, hypertension, LDL-cholesterol, aspirin use, BMI, abdominal visceral fat, diabetes, HDL, CRP, and fasting insulin.

and hemodialysis patients in Italy (26). The largest published study to date was a nested case control study from the Health Professionals Follow-up Study in which 266 primarily White men developed CHD after 6 yr of follow-up (6). Adiponectin remained inversely associated with CHD even after adjusting for potential mediators including HDL, CRP, and glycemia (relative risk, 0.56; 95% CI, 0.32–0.99) (6). Diabetic men in this cohort also had an inverse association of adiponectin with CHD, which was significantly attenuated by HDL-cholesterol (7). However, more recent studies show inconsistent results. In a nested case control from the Strong Heart Study, adiponectin was not associated with incident CHD among Native Americans, irrespective of diabetes status (8). In a nested case-control study of British women, adiponectin was not associated with incident CHD (27). In a cross-sectional study of young adults, adiponectin was positively related to coronary artery calcium score after adjustment for waist circumference and insulin (28). In the Dutch Hoorn Study, adiponectin was inversely associated with nonfatal cardiovascular disease but associated with an increased risk of all-cause mortality (29). Lastly, in a Danish study, higher levels of adiponectin were associated with increased risk of total mortality among patients with congestive heart failure (30). Our findings support the majority of previous findings of a protective association of adiponectin with CHD among White subjects but indicate that high adiponectin may be a potentially harmful independent risk factor for CHD among Blacks.

We found that Black adults have higher levels of HDL-cholesterol and lower levels of triglycerides and abdominal visceral fat than Whites. Racial differences in lipoprotein distribution and body composition are well described (9, 31). Low levels of lipoprotein lipase, a key enzyme involved in lipid metabolism, are associated with a dyslipidemic profile: low HDL and high triglycerides (32). Differences in lipoprotein levels by race are associated with lipase activity and genetic variations in lipoprotein and hepatic lipase genes (33). Blacks had higher lipoprotein lipase activity and reduced hepatic lipase activity compared with Whites in a recent study, suggesting that this increased lipolytic activity in Blacks may contribute to the favorable plasma lipoprotein profile and lower levels of visceral fat (9). Lipoprotein lipase activity was shown to be positively correlated with adiponectin levels independent of CRP and a measure of insulin sensitivity (34). Although unknown, we suspect that the high-molecular-weight form of adiponectin is most related to lipase activity. This line of evidence along with our hypothesis that Blacks may have lower proportions of the high-molecular-weight adiponectin relative to the total circulating adiponectin concentrations raises the possibility that as adiponectin levels increase in Blacks, and relative proportions of high-molecular-weight adiponectin decrease, there may be a down-regulation of lipoprotein lipase activity leading to a less favorable lipoprotein profile and therefore increased risk of CHD in Blacks.

We found no significant difference in total serum adiponectin levels in Blacks with and without incident or prevalent CHD. However, with sequential adjustment of variables in our multivariate models, we observed an increased risk emerge, giving evidence of negative confounding. Without taking these additional metabolic variables into account, we would underestimate the effect of adiponectin with CHD. The fully adjusted serum adiponectin levels for Blacks with incident CHD was 9.22 ± 1.06 μg/ml *vs.* 8.05 ± 1.02 μg/ml for Blacks without incident CHD, which is significantly different.

A strength of this study resides in the measurements of several metabolic factors as well as computed tomography radiographic measures of body composition. However, because Health ABC is a cohort of community-dwelling older adults without advanced physical or cognitive impairment, it is possible that our findings reflect a healthy survivor population that may not generalize to younger adults or more frail elders. Although we followed a large number of participants for several years, we may have had limited power to examine associations with incident CHD in each racial subgroup. Although we may have missed an independent protective effect of adiponectin in Whites, we did find statistical evidence of increased risk of higher adiponectin levels in Blacks.

Even though we have adjusted our incident CHD models for 13 additional variables, we cannot exclude the possibility of residual confounding. Residual confounding could result from using an imperfect surrogate for the true confounder, *e.g.* using fasting insulin and glucose rather than a more precise measure of insulin resistance. Additionally, we may have failed to adjust for other potential confounders. Moreover, the association between adiponectin and CHD in Blacks is of borderline significance and is estimated in a series of models that may inflate the type I error. This is a limitation, and this finding warrants confirmation in future studies of African-American adults.

In conclusion, we found that high serum adiponectin levels were associated with a lower risk of CHD among White men and women, which was attenuated by glucose tolerance, HDL-cholesterol, fasting insulin concentrations, and CRP. However, in Black American men and women, adiponectin was associated with increased risk for CHD after accounting for other known modulators of CHD risk. If this finding is confirmed in future studies, it raises the possibility of different mechanisms by which adiponectin may affect CHD risk that is independent of lipoprotein or glucose metabolism.

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